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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/632,428 | 08/01/2003 | David Bebbington | 030682.0001-US01 | 4377 |

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COVINGTON & BURLING, LLP
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| EXAMINER | |
|---|---|
| RAO, DEEPAK R | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1624 | |

DATE MAILED: 10/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/632,428 | BEBBINGTON ET AL. | |
| | Examiner | Art Unit | |
| | Deepak Rao | 1624 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-7, 9-10, 12-15, 17-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,10,12-15 and 17-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20060803 & 20030801*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

This office action is in response to the amendment filed on August 3, 2006.

Claims 1-7, 9-10, 12-15 and 17-26 are pending in this application.

***Withdrawn Rejections/Objections***:

Applicant is notified that any outstanding rejection/objection that is not expressly maintained in this office action has been withdrawn or rendered moot in view of applicant's amendments and/or remarks.

***The following rejections are maintained***:

Claims 1-7, 9-10, 12-15 and 17-18 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 34-56 of copending Application No. 10/464,430, for the reasons provided in the previous office action which are incorporated here by reference.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

It is acknowledged that 'applicants request the rejection be held in abeyance until one of the applications is in condition for allowance'.

***The following rejections are under new grounds***:

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-7, 9-10, 12-15 and 17-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound of formula **IIIa** or the pharmaceutically acceptable salt thereof, does not reasonably provide enablement for a pharmaceutically acceptable **derivative** or **prodrug** of a compound of formula **IIIa**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claims recite "A compound ... or a pharmaceutically acceptable **derivative** or **prodrug** thereof" wherein there is insufficient description in the specification regarding the types of **derivatives** and **prodrugs** intended by the recitation. The specification provides that the term 'pharmaceutically acceptable **derivative or prodrug** means any pharmaceutically acceptable salt, ester, salt of an ester or other derivative of a compound of the invention which, upon

administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof' (see page 28). The specification describes 'pharmaceutically acceptable salts' that are derived from pharmaceutically acceptable inorganic and organic acids and bases. The terms 'derivative' or 'prodrug' generally represent any type of ester, amide, active metabolite, residue, etc. of a compound. In the instant case, the specification does not provide what 'types of derivatives or prodrugs' of the compounds of formula **IIIa** are intended. The structural formula **IIIa** is a specific structural representation having specific defined substituent groups. There is no disclosure regarding any acid/ester or other **derivatives** of compounds of formula **IIIa** disclosed in the specification. Similarly, the term 'prodrug' is not sufficiently described. A 'prodrug' is any compound which is pharmaceutically active *in vivo* when it undergoes transformation and the specification does not provide any disclosure of what these compounds might be that *in vivo* transform in to the instantly claimed compounds.

It is suggested that the recitation "pharmaceutically acceptable derivative or prodrug" be replaced with -- pharmaceutically acceptable salt -- in all occurrences, throughout the claims.

2. Claims 12-14 and 24-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating diabetes, does not reasonably provide enablement for a method of inhibiting Aurora-2, GSK-3 or Src activity in a biological sample; or a method of inhibiting Aurora-2 activity in a patient; or a method of enhancing glycogen synthesis or lowering blood levels of glucose in a patient; or a method of inhibiting the production of hyperphosphorylated Tau protein in a patient; or a method of inhibiting the

phosphorylation of β-catenin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claim 12 is drawn to 'a method of inhibiting Aurora-2, GSK-3 or Src activity in a biological sample' and the term "biological sample" as per the definition in the specification (page 16, lines 6-11) "includes, without limitation, cell cultures or extracts thereof; preparation of an enzyme suitable for *in vitro* assay; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof". Claims 13-14 are drawn to 'a method of inhibiting Aurora-2 activity in a patient'. Claims 24-26 are drawn to 'a method of enhancing glycogen synthesis or lowering blood levels of glucose', 'a method of inhibiting the production of hyperphosphorylated Tau protein', and 'a method of inhibiting the phosphorylation of β-catenin' in a patient. First, the instant claims appear to be 'reach through' claims. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through to the corresponding

therapeutic method of any or all diseases, disorders or conditions, for which they lack written description and enabling disclosure in the specification thereby requiring undue experimentation for one of skill in the art to practice the invention.

As can be seen from the definition of the term "biological sample", without limitation reads on many and all types of biological samples, which can include mammals or animals and therefore, the claimed method is seen to encompass an inhibitory method wherein the compound is administered to an animal. This is further evident from the purpose of the inhibition activity of the various kinases stated in page 16-23, which includes for example, treatment of a variety of diseases when the methods are applied to a patient or for blood transfusion, organ-transplantation, etc. in the case of a biological sample. As the kinase inhibition activity in a biological sample is seen to be useful for blood transfusion, organ-transplantation, etc., it implicitly reads on the inherent therapeutic methods characterized by the activity, which as per the specification includes numerous types of disorders.

The testing assays provided in the specification at pages 311-320 is to test the ability of the compounds to inhibit GSK-3, Aurora-2, SRC activity using a standard coupled enzyme system, however, there is insufficient guidance in the disclosure regarding the provided assay. There is no indication of the tests required for the other activities recited in the claims such as 'enhancing glycogen synthesis', 'lowering blood levels of glucose', 'inhibiting the production of hyperphosphorylated Tau protein' or 'inhibiting the phosphorylation of $\beta$-catenin'. Further, all compounds for which the activity related to some of the kinase inhibition is indicated, are structurally distinct from the instant claims, i.e., the activity is reported to compounds wherein ring A is pyrimidinyl group as compared to the instant claims wherein ring A is pyridinyl. First,

the specification provides that the coupled enzyme system is provided in Fox et al., however, the cited article deals with inhibition of p38 MAP kinase activity. Next, applicant has not provided how this correlates with the efficacy in all types of biological samples encompassed by the instant method and their use in the various purposes wherein the inhibition activity is useful. For example, blood transfusion is the process of transferring blood or blood-based products from one person into the circulatory system of another. Blood transfusions may be seen as a procedure to treat some medical conditions, such as massive blood loss due to trauma, surgery, shock and where the red cell producing mechanism (or some other normal and essential component) fails. Similarly, an organ transplantation is the transplantation of a whole or partial organ from one body to another (or from a donor site on the patient's own body), for the purpose of replacing the recipient's damaged or failing organ with a working one from the donor site. As can be seen from the above, without limitation these purposes are intended for therapeutic methods and applicant has not provided competent evidence sufficient to enable the claimed method.

The instant claims are read on many therapeutic methods, for example, a method of treating cancer, Alzheimer's disease, autoimmune diseases, etc. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). A 'disorder characterized by abnormal cell proliferation' is anything that is caused by abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or

continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers or abnormal cell proliferative disorders generally.

Further, there is no disclosure regarding how the patient in need of the treatment requiring the specific kinase (i.e., Aurora-2, GSK-3, Src) inhibiting activity is identified and further, how all types of the diseases having divers mechanisms are treated. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, and the data provided of the single compound is insufficient for one of ordinary skill in the art in order to extrapolate to the other compounds of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims. The state of the art is indicative of the unpredictability of the therapeutic approach based on kinase inhibiting activity. Hardt et al. (Circulation Research 2002) indicate that there are many unanswered questions regarding the GSK-3 function and the signaling mechanisms remain to be determined, see the article.

Further, there is no disclosure regarding how the patient in need of such specific kinase inhibiting activity is identified and further, how types of cardiovascular diseases, autoimmune diseases, Alzheimer's disease, schizophrenia, etc. are treated. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, and the data provided of the single compound is insufficient for one of ordinary skill in the art in order to extrapolate to the other compounds of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims. The state of the art is indicative of the unpredictability of the therapeutic approach based on kinase inhibiting activity. "How sister kinetochores attach to microtubules from opposite spindle poles during mitosis (bi-orientation) remains poorly understood", see Tanaka et al. (PubMed Abstract enclosed). Also, Rogers et al., express that "How the selective release of chromosome cohesion is regulated during meiosis remains unclear". This is clearly indicative of the fact that the therapeutic role of kinase inhibitors is very speculative.

There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein and therefore, require the treatment. Next, applicant's attention is drawn to the "Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001" wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly intended 'treating of a disease or disorder' solely based on the kinase inhibitory activity disclosed for the compounds.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

***Double Patenting***

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-7, 9-10, 12-13 and 24-26 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-7, 9-10, 12-13 and 19-21 of prior U.S. Patent No. 6,664,247. This is a double patenting rejection.

The instant claim 1 recites "A compound of formula IIIa or a pharmaceutically acceptable derivative or prodrug thereof", wherein the terms "derivative" and "prodrug" are subject to a rejection under 35 U.S.C. 112, 1st paragraph (see the rejection above). If the claims are amended to replace the recitation with -- pharmaceutically acceptable salt -- to overcome the enablement rejection, then claim 1 would be of the same scope as reference claim 1.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1. Claims 1-7, 9-10, 12-15 and 17-26 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 6,664,247. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims substantially overlap the compounds of the reference claims, see the claims in each of the application. Claims 1-7, 9-10, 12-13 and 24-26 are almost identical to reference claims, see the rejection above. Claims 14-15 and 17-23 slightly differ in scope from the reference claims 14-18. It would have been obvious to one having ordinary skill in the art at the time of the invention to use the compounds in any of the methods taught by the reference, including those instantly claimed, because the skilled artisan would have had the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as pharmaceutical therapeutic agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole.

2. Claims 1-7, 9-10, 12-15 and 17-18 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 34-56 of copending Application No. 11/500,981. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims substantially overlap the compounds of the reference claims, see the claims in each of the application. It would have been

obvious to one having ordinary skill in the art at the time of the invention to select any of the compounds from the reference claims and/or use the compounds in any of the methods taught by the reference, including those instantly claimed, because the skilled artisan would have had the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as pharmaceutical therapeutic agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Duplicate Claims***

1. Applicant is advised that should claim 21 be found allowable, claim 19 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Instant claim 19 is a mode of action claim which relates to treatment of the diseases. Applicant's attention is drawn to the court decision, wherein the court held that double patenting applies between a claim reciting mode of action and a claim reciting treatment of a disease, if the connection between the two would be apparent to one of ordinary skill in the art. See *Lilly vs. Barr*, 58 USPQ2d 1869, at 1879.

2. Applicant is advised that should claim 20 be found allowable, claim 22 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 22 does not further limit claim 20.

***Claim Objections***

Claims 19-22 are objected to because of the following informalities:

The claims recite "amyotrophic lateral sclerosis (**AML**)" wherein the abbreviation "AML" is not appropriate for the disease stated. The disease "amyotrophic lateral sclerosis" is abbreviated as -- **ALS** -- (see http://en.wikipedia.org/wiki/Amyotrophic_lateral_sclerosis) whereas the abbreviation 'AML' represents 'acute myeloid leukemia' (see http://en.wikipedia.org/wiki/Acute_myeloid_leukemia). Appropriate correction is required.

Receipt is acknowledged of the Information Disclosure Statement filed on August 3, 2006 and a copy is enclosed herewith.

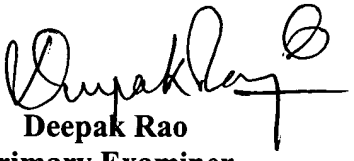
***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



**Deepak Rao**
**Primary Examiner**
**Art Unit 1624**

October 25, 2006